

The University of Chicago

STUDIES IN THE HYDURILIC ACID SERIES

A DISSERTATION SUBMITTED TO THE FACULTY
OF THE DIVISION OF THE PHYSICAL SCIENCES
IN CANDIDACY FOR THE DEGREE OF DOCTOR
OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

1937

By

ALBERT VIRGIL WILLETT, JR.

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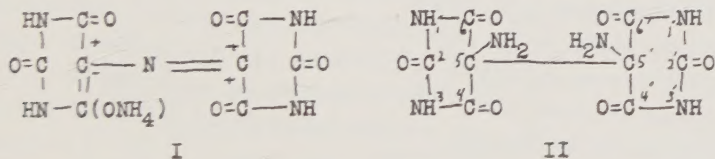
I. INTRODUCTION

Since 1904, the accepted structure of murexide has been that proposed simultaneously by Slimmer and Stieglitz,¹ Piloty and Finckh,² and Möhlau.³ This structure, the ammonium salt of purpuric acid (I), is in complete agreement with the known reactions of murexide. Murexide is readily hydrolyzed by aqueous acids, to form uramil, $\text{CO-NH-CO-NH-CO-CH(NH}_2\text{)}$, and alloxan, CO-NH-CO-NH-CO-CO . It is a salt, and its solutions exhibit salt-like conductance of the electric current. Murexide may be formed by the condensation of alloxan and uramil. Two isomeric dimethylmurexides may be formed by the condensation of dimethylalloxan and uramil, and by the condensation of dimethyluramil and alloxan. These facts and the intense color of the compound are consistent with structure I.

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An inspection shows that, according to the Stieglitz opinion, such a compound would be expected to have an intense color. The reduced component is the one containing the more electronegative carbon atom, while the oxidized component is the one containing the more electropositive carbon atom; the structure is that of a salt.



¹Slimmer and Stieglitz, Am. Chem. Journal, **36**, 661-79 (1904).

²Piloty and Finckh, Ann., **333**, 84 (1904).

³Möhlau, Ber., **37**, 2686 (1904).

Recently, Davidson¹ proposed another structure (II) for murexide. This structure does not explain the instability of murexide toward aqueous acids, its hydrolysis to alloxan and uramil, and its salt like electrolytic conductivity; it also does not explain the formation of two isomeric dimethylmurexides. A compound of this structure, if the Stieglitz theory of color is correct, should be colorless, since it is electronically symmetrical, and has neither oxidizing nor reducing components.

If Davidson's structure for murexide is correct it would cast some doubt on the Stieglitz theory of color production. Therefore, a further test of Davidson's structure is of interest and this investigation was undertaken with the intention of synthesizing the compound, 5,5'-diaminohydurilic acid, by preparation of the acid followed by the introduction of the two amino groups. Should the compound so synthesized be identical with murexide, Davidson's structure would be confirmed. Furthermore, even if the compound so obtained, though not identical with murexide, should have intense color, the result would be difficult to reconcile with the Stieglitz theory.

After this dissertation was undertaken, but before its completion, Davidson, following his synthesis of leucomurexide,^{2,3,4} withdrew his support of structure II. This compound, which was shown to be ammonium dihydro purpurate, is easily oxidized by air to murexide, from which it is prepared by reduction by sodium hydrosulfite. The reduction of murexide to colorless leucomurexide is typical of the behavior of all dyes toward reduction.

Although structure II had been conclusively shown to be incorrect as the structure for murexide, the problem of its color still seemed of interest sufficient to warrant the continuation of the investigation.

II. DISCUSSION OF RESULTS

The objective of the research was the preparation of

¹Davidson, Private communication to Professor Stieglitz.

²Davidson, J.A.C.S., 58, 1822 (1936).

³Davidson, J. Org. Research, 1, 305 (1936).

⁴Davidson, Private communication to Professor Stieglitz.

5,5'-diaminohydurilic acid. Two general methods were attempted-- one, to introduce two amino groups directly into hydurilic acid, and the other to introduce nitroso groups into the 5,5' positions, which were then to be reduced. As will appear, neither method led to the desired results, but information of value regarding the properties of hydurilic acid and its derivatives was obtained.

The first step in the investigation was an attempt to improve the method of preparation of hydurilic acid itself. The usual methods of condensing urea with esters were not available in this case. Roeder¹ had found that, in the presence of sodium ethylate, dimalonic ester condensed with urea to form a di-imide instead of the diureide, hydurilic acid. Conrad² showed that urea and phosphorus oxychloride did not react with dimalonic ester, since the ester groups were not attacked. Also condensation by heating with phosphorus pentachloride was not possible since decomposition occurs.

It was suggested that the condensation of dimalonic ester and ethyl isourea might result in the formation of hydurilic acid. The condensation was tried and two products were obtained. Of these, one contained 39.83 per cent nitrogen; the other contained 28.17 per cent nitrogen. Since hydurilic acid contains 22.05 per cent nitrogen it was apparent that this method of preparation is not feasible.

Because of the lack of success with this method attention was next turned toward improvements in the desulfurization of dithiohydurilic acid. Although various methods, involving the use of litharge, litharge and sodium hydroxide, mercuric oxide, and mercuric acetate, were investigated, the results were not sufficiently encouraging to follow this line of experimentation further, since in no case did complete desulfurization take place.

Consequently the next step was the preparation of dichlorohydurilic acid and efforts to replace the chlorine atoms by amino groups. Three methods were used.

Biltz³ had shown that dehydrohydurilic acid reacts with ammonium hydroxide to produce 5-aminohydurilic acid, which can be reduced to uramil and barbituric acid. Therefore, a small sample

¹Roeder, Ber., 17, 2781 (1884).

²Conrad, Ann., 214, 70 (1882).

³Biltz, Ber., 52, 1308 (1919).

of 5,5'-dichlorohydurilic acid was allowed to stand in concentrated ammonium hydroxide over night. No reaction took place and the original material was recovered.

Although dichlorohydurilic acid had failed to react with ammonium hydroxide, it was thought possible that it might react with ammonia itself. However, a sample allowed to stand in liquid ammonia in an unsilvered Dewar flask until the ammonia had evaporated was recovered unchanged.

There was still the possibility that there might be a reaction with liquid ammonia at higher temperatures and pressures than those afforded by boiling liquid ammonia. Therefore, dichlorohydurilic acid was sealed in a bomb containing liquid ammonia, and allowed to stand for ten days. At the end of this time the bomb was opened and the ammonia boiled off. Again dichlorohydurilic acid was recovered unchanged. Because ten days might not have been a sufficiently long time for the reaction, a small sample was sealed in a bomb with liquid ammonia and examined after twenty-five days, at which time there was some evidence of a reaction. The filtrate from the aqueous suspension of the bomb contents gave a copious silver chloride precipitate when treated with silver nitrate. The reaction was nevertheless abandoned in favor of one involving potassium amide in liquid ammonia.

A small quantity of dichlorohydurilic acid was allowed to remain in contact with potassium amide in liquid ammonia at room temperature for six weeks in a sealed bomb tube. At the end of this time the contents had a uniform red color, but consisted of two major portions; the first portion soluble in cold water and the second portion soluble in hot water. From each of these fractions several substances were obtained.

The portion soluble in cold water was separated into a compound identified as alloxan monohydrate (17.50 per cent nitrogen) since it contained 17.59 per cent nitrogen and showed the red skin test, blue ferrous ammonium sulfate test, and red coloration with ammonia characteristic of alloxan, and a red substance of unknown composition.

The second major portion was dissolved in hot water and the resulting solution was divided into four portions. From these fractions four substances of unknown character were obtained by treatment with silver nitrate, alcohol, hydrochloric acid, and slow evaporation respectively. Since none of the substances was

the desired 5,5'-diaminohydurilic acid, which contains 29.58 per cent nitrogen, further investigation of these products was discontinued.

Although it had not been found possible to substitute two amino groups for the 5,5' halogen atoms in dichlorohydurilic acid by means of potassium amide and liquid ammonia, it was possible that the difficulty had been caused by enolization of the urea hydrogen atoms. It was thus of interest to study the reaction between tetramethyldichlorohydurilic acid and sodium amide in liquid ammonia.

Accordingly a small bomb which contained 1,3,1',3',-tetramethyl-5,5'-dichlorohydurilic acid, sodium amide, and liquid ammonia was allowed to stand for seven months. From the contents of this bomb two products were obtained. One of these was soluble in water and contained a trace of nitrogen. With uranyl acetate the material gave a profusion of tetrahedra, a characteristic test for sodium ion. The second material was soluble in alcohol and contained neither nitrogen nor chlorine. The reaction did not yield the desired tetramethyldiaminohydurilic acid and the products obtained did not seem to be of sufficient interest to warrant continuing the investigation.

In place of direct amination of hydurilic acid the introduction of nitro groups into the 5,5' positions followed by their reduction to the amino compound might be considered, but it is not possible since Baeyer¹ had shown that hydurilic acid reacts with concentrated nitric acid to form violuric acid, violantine, and dilituric acid. This leaves the introduction of nitroso groups as a possibility.

Sodium nitrite was the first reagent used in the attempt to introduce two nitroso groups into the 5,5' positions. A small sample of hydurilic acid was dissolved in hot water and allowed to react at 50°, with an aqueous solution of sodium nitrite. At the end of three hours the solution had developed its maximum color, a rich purple red. Hydrogen sulfide was bubbled through the solution until the color had disappeared. From the reaction mixture, sulfur and a substance containing 19.62 per cent nitrogen were obtained. The latter material may have been sodium diliturate monohydrate (19.71 per cent nitrogen) which is not re-

¹Baeyer, Ann., 127, 199 (1863).

ducible by hydrogen sulfide. Since the substance was not diamino-hydurilic acid (29.58 per cent nitrogen) it was necessary to repeat the reaction in order to attempt the isolation of the nitroso compound.

An excess of sodium nitrite solution was added to an aqueous suspension of hydurilic acid at 15°. The hydurilic acid dissolved and the solution became a rich red and was slightly alkaline. Evaporation of the mixture at room temperature led to the formation, in twenty-four hours, of a red precipitate. This was removed from the remaining solution; the purified product contained 21.35 per cent nitrogen. It is believed to be sodium violurate monohydrate (21.32 per cent nitrogen).

When a portion of the mother liquor was reduced with stannous chloride a yellow solid was obtained. This material contained 26.73 per cent nitrogen, and with alloxan and ammonium carbonate showed the red color of murexide solutions. This behavior is typical of uramil. The substance may have been a mixture of 60 per cent uramil (29.58 per cent nitrogen) and 40 per cent barbituric acid (21.90 per cent nitrogen).

The results of this action are not entirely unexpected since Baeyer¹ had shown that hydurilic acid reacts with potassium nitrite and acetic acid to form potassium violurate and alloxan. However, in our investigation the reaction was carried out without the addition of acid. The hydurilic acid itself was probably strong enough to give a typical nitrous acid reaction with sodium nitrite.

If the inherent acidity of hydurilic acid could be suppressed sodium nitrite might react to introduce nitroso groups. Thus if the enolizable urea hydrogen atoms were replaced by the substitution of methyl groups and the 5,5' positions were occupied by halogens which could later be removed by a metal, the desired reaction might proceed. Therefore tetramethyldichlorohydurilic acid was chosen for the next attempt.

An acetone solution of tetramethyldichlorohydurilic acid was refluxed with an aqueous solution of sodium nitrite until the solution became a deep rose red. From the solution of red crystalline precipitate was obtained, and was shown to be sodium dimethyl violurate trihydrate by the following tests:

¹Baeyer, Ann., 127, 200 (1863).

- 1) Its nitrogen content is 14.38 per cent).
- 2) It gives the uranyl acetate test for sodium ion.
- 3) Its silver salt contains 37.16 per cent silver and 13.74 per cent nitrogen (theoretical 36.98 per cent silver and 14.38 per cent nitrogen).
- 4) It forms, upon treatment with glacial acetic acid, an orange yellow acid sodium salt as does sodium dimethylviolurate.

The presence of dimethylalloxan was detected in the acetone filtrate by means of its characteristic red skin test (formation of murexide), and by means of the blue ferrous ammonium sulfate test. No other products were obtained.

Although sodium nitrite had not introduced two nitroso groups into the tetramethyldichlorohydurilic acid, but had broken the 5,5' carbon to carbon bond, it was thought possible that, by removal of halogen atoms by means of silver, the two groups could be introduced. Consequently two samples of tetramethyldichlorohydurilic acid, one suspended in water and one dissolved in benzene, were shaken with silver nitrite for twenty-four hours. At the end of the shaking period both samples of tetramethyldichlorohydurilic acid were recovered unchanged. This may have been due to the insolubility of the silver nitrite.

None of the eight methods described resulted in the formation of the desired 5,5'-diaminohydurilic acid or its tetramethyl derivative. However, some information of value was obtained concerning the properties of hydurilic acid and its derivatives, namely, the production of alloxan by the reaction between dichlorohydurilic acid and potassium amide in liquid ammonia, the formation of sodium violurate and alloxan from hydurilic acid and sodium nitrite, and the quite unexpected reaction between tetramethyldichlorohydurilic acid and sodium nitrite to form sodium dimethylviolurate and dimethylalloxan.

III. EXPERIMENTAL PART

1. Preparation of Dimalonic Ester (Ethyl Ethanetetra-carboxylate), $(\text{COOC}_2\text{H}_5)_2\text{CH}-\text{CH}(\text{COOC}_2\text{H}_5)_2$

The laboratory procedure for the preparation of dimalonic

ester was that described by Bischoff.¹ Sodium (7 g.) was dissolved in 250 cc. of absolute alcohol. To this solution ethylmalonate (50 g.) was added slowly; upon addition of the last portion, the solution solidified into a white jelly-like mass. This was dissolved by adding more alcohol, warming, and shaking. The solution was then cooled and ether was added until a slight turbidity appeared. Iodine (40 g.) dissolved in 250 cc. of ether was then added in small portions while violently shaking the flask containing the sodium malonate mixture.

The solution, deeply colored by excess iodine, was extracted with water to remove sodium iodide, the ethereal and aqueous layers were separated, and both were decolorized with sodium thiosulfate. Evaporation of the ether solution left as a residue an oil which solidified when cooled. The product was dimalonic ester. An additional small quantity was obtained from the aqueous layer. The total yield was 36.5 g. or about 75 per cent. The material had a melting point of 76°.

2. Condensation of Dimalonic Ester with Ethylisourea

Ethylisourea was prepared from ethylisourea hydrochloride by Terre's² method. Ethylisourea hydrochloride was moistened with water, and covered with 200 to 300 cc. of alcohol free ether and cooled in an ice and salt bath. Powdered potassium hydroxide (4-5 mols / mol of isourea hydrochloride) was added slowly with constant stirring. The ether was poured off and the residue was extracted five or six times with ether. The ether extracts were combined and the ether was evaporated off leaving an oil. This oil, which was identified as ethyl isourea, was dried in a vacuum dessicator over concentrated sulfuric acid and solid potassium hydroxide.

The method used for the condensation of dimalonic ester and ethyliso urea was essentially that of Terre.³ Dimalonic ester in ether solution (10 g., 1 mol) was added to ethyl isourea (10.65 g., 4 mols) and placed in a vacuum dessicator over concentrated sulfuric acid and solid potassium hydroxide, and allowed to stand for four days. The sulfuric acid was changed after two

¹Bischoff, Ber., 17, 2781 (1884).

²Terre, M.S. Dissertation, University of Chicago, 1932.

³Ibid.

days, at which time a strong odor of ammonia was noticed.

The reaction product was washed with ether, filtered, and washed with alcohol. The filtrate was evaporated to half volume and diluted with water acidified with hydrochloric acid. Dimalonie ester was then recovered in the form of white needles. The aqueous filtrate, after removing dimalonie ester, was evaporated to dryness. This yielded a peach colored precipitate. This substance, after reprecipitation from hot water, contained 28.17 per cent nitrogen.

The reaction product, after it was washed with alcohol, was dissolved in water acidified with hydrochloric acid. The solution was heated, ethyl chloride was evolved and detected by means of its characteristic green flame, and a gray white precipitate appeared. This material was reprecipitated from hot water and found to contain 39.83 per cent nitrogen. Neither this substance nor the peach colored substance melted, but charred and decomposed upon heating to a high temperature. Neither was identified.

3. Preparation of 2,2'-dithiohydurilic Acid

Dithiohydurilic acid was prepared according to Roeder's method.¹ Dimalonie ester (16 g.) and thiourea (8 g.) were refluxed for seven hours in a solution containing sodium (4.6 g.) in 150 cc. of absolute alcohol. During the last half hour 100 cc. more of absolute alcohol were added. The suspension was filtered hot and washed with hot alcohol. The cream colored solid was dried on the steam bath and powdered. It was then dissolved in warm water (50°) giving an orange red colored solution. Upon addition of concentrated hydrochloric acid (50 cc.) a precipitate began to appear. The suspension was cooled, filtered, and the precipitate washed with dilute hydrochloric acid, alcohol, and ether. The yield was 8 g. or 57 per cent. This material when treated with a solution of ferric chloride shows a deep green color characteristic of hydurilic acid compounds.

4. Desulfurization of Dithiohydurilic Acid

Mercuric oxide (3 g.) was added to dithiohydurilic acid (4 g.) suspended in water. The mixture was then heated on the

¹Roeder, loc. cit.

steam bath and stirred mechanically for twenty-four hours. The resulting black mercuric sulfide was separated from the liquid which was treated with concentrated hydrochloric acid (25 cc.). The white precipitate so obtained was fused with sodium, and the resulting melt was extracted with alcohol and water; the extract gave a strongly positive test for sulfur. At no time was it found possible to remove sulfur completely from dithiohydric acid by means of mercuric oxide.

Similar procedures were employed in attempts to desulfurize dithiohydric acid by means of mercuric acetate, litharge, and litharge and sodium hydroxide. None of these reagents accomplished a complete desulfurization.

Roeder's¹ was the only successful method found for desulfurizing this compound. Dithiohydric acid (1.8 g.) was placed in concentrated sulfuric acid (22 g.) and heated on the steam bath for eight to ten hours. The solution was cooled overnight and decanted from the resulting precipitate. The latter was boiled with water, and the sulfur was removed. From the chilled filtrate sulfur free hydric acid precipitated. This method of desulfurizing gives very low yields (about 33 per cent) but was the only one giving pure hydric acid.

5. Preparation of 5,5'-Dichlorohydric Acid

Dichlorohydric acid was prepared by each of the methods described by Biltz and Hamburger.² By means of the first method hydric acid (3 g.) was mixed to a paste with 3 cc. of concentrated hydrochloric acid. Powdered potassium chlorate (1.5 g.) was added with stirring, and chlorine was evolved. The yield was about 80 per cent.

The second method was found to be more efficient since it gave a yield of about 98 per cent. Hydric acid (5 g.) was dissolved in 60 cc. of hot alcohol. The solution was cooled with ice, causing precipitation of the hydric acid. A strong stream of chlorine was bubbled through until the suspension had completely dissolved. The solution was heated until turbid, diluted with water and further heated until precipitation was complete.

¹Ibid.

²Biltz and Hamburger, Ber., 49, 656 (1916).

6. The Treatment of 5,5'-Dichlorohydurilic Acid with Liquid Ammonia

Dichlorohydurilic acid (1 g.) was placed in a glass bomb and the tube filled one third full with liquid ammonia. The bomb was then cooled in a dry ice and acetone bath. When the liquid ammonia had solidified, the bomb was sealed and placed in a steel bomb jacket, in which it was allowed to stand for ten days. At the end of this time the bomb was removed, chilled in a dry ice and acetone bath, and opened. After the ammonia had been removed by slow evaporation the residue in the bomb was washed with very dilute hydrochloric acid. When dried it charred but did not melt. It was analyzed for nitrogen and thus shown to be unchanged dichlorohydurilic acid:

1.362 mg. of sample gave 0.205 cc. of gas
at 24° and 752.2 mm. (corr.)

Calculated for $C_8H_4O_6N_4Cl_2$, N: 17.39 per cent
Found, N: 17.21 per cent

Another bomb was prepared in the same way and allowed to stand for twenty-five days. After removal of ammonia, the residue was then leached with water. The resulting extract was acidified with nitric acid and treated with silver nitrate. A precipitate of silver chloride was formed immediately. Evidently some reaction had taken place, but the residue was not investigated further.

7. The Reaction between 5,5'-Dichlorohydurilic Acid and Potassium Amide in Liquid Ammonia at Room Temperature

Potassium (1 g.) was dissolved in about 50 cc. of liquid ammonia and converted into potassium amide by use of a rusty spiral of iron wire which acts as a catalyst. Dichlorohydurilic acid (4 g.) was added and the bomb containing the mixture was sealed and placed in a steel jacket. The bomb was allowed to stand for six weeks.

At the end of this time the contents were of a uniform purple red color. The reaction product was washed with about 5 cc. of ice water and the residue separated from the water by filtration. The filtrate, with silver nitrate gave a heavy precipitate of silver chloride. The material was next washed with water at room temperature (about 20 cc.) and the residue saved.

Acetone was added to the aqueous filtrate and a gummy red substance was formed. This material was dissolved in a small amount of water at room temperature and alcohol was added. A voluminous red precipitate was formed. The clear supernatant solution was removed by filtration and saved. The red substance gave a negative Beilstein test and a negative test for potassium by Fiegel's method.¹ The material contained only 18.75 per cent of nitrogen and consequently was not the desired diaminohydurilic acid (nitrogen content 29.58 per cent).

0.845 mg. of sample gave 0.138 cc. of gas
at 24° and 752.8 mm. (corr.)

1.562 mg. of sample gave 0.260 cc. of gas
at 26° and 752.8 mm. (corr.)

1.664 mg. of sample gave 0.284 cc. of gas
at 28° and 739.3 mm. (corr.)

Found, N: 18.60 per cent, 18.83 per cent, 18.83 per cent

The alcoholic filtrate from the red substance was evaporated to dryness yielding a yellow white solid. This was recrystallized from a little water. The material gave a red skin test, a red color with ammonia and a blue ferrous ammonium sulfate test. The compound is believed to be alloxan. It was analyzed for nitrogen:

1.950 mg. of sample gave 0.304 cc. of gas
at 26° and 750.1 mm. (corr.)

2.126 mg. of sample gave 0.331 cc. of gas
at 25.5° and 751.5 mm. (corr.)

Calculated for $C_4H_4O_5N_2$, N: 17.50 per cent

Found N: 17.57 per cent, 17.61 per cent

The residue insoluble in water at room temperature was dissolved in hot water to a red solution. This solution was divided into four portions. Three of these were treated immediately with silver nitrate, alcohol, and dilute hydrochloric acid respectively. The fourth portion was allowed to evaporate slowly. The products obtained are all of unknown character and differ from diaminohydurilic acid as seen from their properties and analyses which are given below in order:

¹Fiegel, "Tupfelreactionen," p. 215.

A. Amber gel containing an undetermined amount of chlorine

1.760 mg. of sample gave 0.884 mg. of silver
1.374 mg. of sample gave 0.688 mg. of silver

5.117 mg. of sample gave 0.407 cc. of gas
at 25° and 738.2 mm. (corr.)

2.433 mg. of sample gave 0.185 cc. of gas
at 27° and 750.2 mm. (corr.)

Found, Ag: 50.23 per cent, 50.05 per cent
N : 8.65 per cent, 8.54 per cent

B. Pink precipitate containing potassium but no chlorine

1.801 mg. of sample gave 0.214 cc. of gas
at 26.5° and 754.8 mm. (corr.)

Found N: 13.45 per cent

C. White crystalline solid containing an unknown amount of chlorine

1.516 mg. of sample gave 0.196 cc. of gas
at 25.5° and 753.3 mm. (corr.)

1.484 mg. of sample gave 0.194 cc. of gas
at 25° and 754.5 mm. (corr.)

1.585 mg. of sample gave 0.203 cc. of gas
at 26° and 754.5 mm. (corr.)

Found, N: 14.66 per cent, 14.87 per cent, 14.52 per cent

D. White, well formed, monoclinic crystalline precipitate containing chlorine

1.867 mg. of sample gave 0.255 cc. of gas
at 27° and 747.2 mm. (corr.)

1.540 mg. of sample gave 0.211 cc. of gas
at 26° and 736.5 mm. (corr.)

Found, N: 15.28 per cent, 15.16 per cent

8. Reaction between Hydruilic Acid and Sodium Nitrite

Hydruilic acid (2 g.) was dissolved in a small amount of hot water and placed in a thermostat at 50°. To this solution was added a solution of sodium nitrite (1.1 g.) in water. There was an immediate evolution of nitrogen dioxide. After half an hour had elapsed a deep red color began to appear, which at the end of three hours had deepened to a rich purple red. Hydrogen sulfide was then bubbled through the solution for three hours until all the color had disappeared. The solution was colorless,

but a pink precipitate which did not dissolve in concentrated hydrochloric acid had appeared.

The precipitate was separated from the solution, dried and powdered. It was then placed in dilute hydrochloric acid and heated at 50° until decolorized. The solid remaining in suspension was sulfur, and was removed from the supernatant liquor. The filtrate was cooled, and ultimately gave rise to a pale tan precipitate. Although the nitrogen content of the substance (as shown by the following data) and its failure to be reduced by hydrogen sulfide are characteristics of sodium diliturate monohydrate (19.71 per cent nitrogen), no further corroboration of its structure was attempted.

2.197 mg. of sample gave 0.377 cc. of gas
at 23.5° and 750.7 mm. (corr.)

1.853 mg. of sample gave 0.324 cc. of gas
at 26° and 751.0 mm. (corr.)

Found, N: 19.52 per cent, 19.73 per cent

A solution of hydurilic acid (4.7 g.) in 300 cc. of hot water was cooled to 15° . Precipitation of the hydurilic acid occurred. A solution of sodium nitrite (2.5 g.) was added in small portions with stirring. The solution began to turn pink, and remained acid to litmus. Since the major portion of the hydurilic acid had not reacted an excess of sodium nitrite solution was added until all the precipitate had disappeared and the color was a deep purple red. From this solution a rose red substance precipitated, which was washed with cold water and alcohol. Analysis for sodium and nitrogen suggested that the product is sodium violurate monohydrate.

2.584 mg. of sample gave 0.944 mg. of sodium sulfate
1.840 mg. of sample gave 0.681 mg. of sodium sulfate

2.766 mg. of sample gave 0.522 cc. of gas
at 23.5° and 747.2 mm. (corr.)

1.267 mg. of sample gave 0.240 cc. of gas
at 25.5° and 749.0 mm. (corr.)

Calculated for $C_4H_2O_4N_3Na.H_2O$, Na: 11.68 per cent
N : 21.32 per cent

Found: Na: 11.83 per cent, 11.98 per cent
N : 21.36 per cent, 21.35 per cent

When some of the red solution was reduced with stannous chloride in hydrochloric acid solution a yellow precipitate ap-

peared. This substance reacted with alloxan and ammonium carbonate to give the red color of murexide solutions. This is typical of the behavior of uramil. The substance was analyzed for nitrogen:

2.280 mg. of sample gave 0.549 cc. of gas
at 25° and 740.9 mm. (corr.)

2.170 mg. of sample gave 0.514 cc. of gas
at 25° and 744.0 mm. (corr.)

Found, N: 26.90 per cent, 26.57 per cent

The substance may have been a mixture of 60 per cent uramil (29.37 per cent nitrogen) and 40 per cent barbituric acid (21.90 per cent nitrogen). Both of the products might be expected to be present.

9. Preparation of 1,3,1',3',-Tetramethylhydurilic Acid
and 1,3,1',3',-Tetramethyl-5,5'-dichlorohydurilic Acid

Tetramethylhydurilic acid was prepared by the method of Biltz.^{1,2} Caffeine (25 g.) was dissolved in concentrated hydrochloric acid (35 g.) and 75 cc. of water. The solution was heated at 50° for two hours, during which time powdered potassium chlorate (10 g.) was added bit by bit. After the 8-chlorocaffeine which is formed during the oxidation, was dissolved, the solution was cooled with ice and the dissolved chlorine was pumped off. After two hours apocaffeine and isoapocaffeine precipitated. The solution was separated from these products, and cooled further with ice while a solution of stannous chloride (13.5 g.) in 10 cc. of concentrated hydrochloric acid was added dropwise. Tetramethylalloxantine (17 g.) precipitated.

The latter was heated at 250° in a beaker for three hours. At the end of this time the melt can either be poured into water, or allowed to cool and solidify, and then be placed in water. There seemed to be little difference in the yields. Concentrated ammonium hydroxide converted the mixture into a brown red solution. Biltz recommended that this solution be treated with animal charcoal. It was found, however, that the hydurilic acid formed was deeply colored even if the charcoal was used. Since charcoal re-

¹Biltz, Ber., 45, 3674 (1912).

²Biltz, Ber., 49, 659 (1916).

duced the yield its use is not recommended. The filtrate from this mixture was treated with concentrated hydrochloric acid and gave a precipitate of tetramethylhydurilic acid. The yield is rather low.

From the tetramethylhydurilic acid thus prepared the dichloro derivative was obtained by the method of Biltz and Hamburger.¹ A strong stream of chlorine was passed into a refluxing solution of tetramethylhydurilic acid (5 g.) in 100 cc. of chloroform. Hydrogen chloride was evolved. The reaction was complete in about twenty minutes. Air was then passed through the solution until it was free of chlorine. The chloroform was evaporated off on the steam bath, and the resulting tetramethyldichlorohydurilic acid was recrystallized from glacial acetic acid. The yield was quantitative.

10. Reaction between 1,3,1',3',-Tetramethyl-5,5'-dichlorohydurilic Acid and Sodium Nitrite

Tetramethyldichlorohydurilic acid (1 g.) was dissolved in 50 cc. of acetone. To this was added sodium nitrite (0.5 g.) dissolved in a small amount of water. The material was refluxed for about twenty minutes. The solution became a rich violet red color, and nitrogen dioxide was noticed at the top of the reflux condenser. The solution was cooled, and the violet red precipitate resulting was removed by filtration. The precipitate was recrystallized from a small amount of boiling water.

The violet red crystals gave a positive test for sodium ion with uranyl acetate, were transformed into an orange yellow solid when treated with acetic acid, and had the following nitrogen content:

1.842 mg. of sample gave 0.265 cc. of gas
at 26.5° and 739.3 mm. (corr.)

2.204 mg. of sample gave 0.327 cc. of gas
at 31° and 734.2 mm. (corr.)

Found N: 15.96 per cent, 16.10 per cent

All of these properties indicate it to be sodium dimethylviolurate trihydrate (nitrogen content, 16.10 per cent). This conclusion was confirmed by the formation of its easily decompos-

¹Biltz and Hamburger, loc. cit.

ible silver salt, the analysis of which follows:

2.665 mg. of sample gave 1.003 mg. of silver
1.244 mg. of sample gave 0.456 mg. of silver
1.375 mg. of sample gave 0.511 mg. of silver

3.301 mg. of sample gave 0.405 cc. of gas
at 26° and 745.4 mm. (corr.)

Calculated for $C_6H_6O_4N_3Ag$, Ag: 36.98 per cent
N : 14.38 per cent

Found, Ag: 37.64 per cent, 36.66 per
cent, 37.16 per cent
N : 13.74 per cent

Upon evaporation of the acetone filtrate to half volume some tetramethyldichlorohydurilic acid was recovered. The filtrate was shown to contain dimethylalloxan by the red skin test, and the blue color produced by ferrous ammonium sulfate.

11. Reaction between Tetramethyldichlorohydurilic Acid and Sodium Amide in Liquid Ammonia at Room Temperature

Tetramethyldichlorohydurilic acid (1 g.) was sealed in a bomb with sodium amide and liquid ammonia, and allowed to stand for seven months. The contents of the bomb after evaporation of the ammonia were then extracted with water. The extract was evaporated to dryness and the residue reprecipitated from the least amount of hot water. This was a yellowish white material which gave a strongly positive test for sodium ion with uranyl acetate, and contained a trace of nitrogen. The amount of the latter was too small for measurement.

The portion insoluble in water was soluble in alcohol and was reprecipitated from that solvent. It was found to contain neither chlorine nor nitrogen.

SUMMARY

1. The reaction between ethylisourea and ethylethanetetra-carboxylate, which did not yield the desired hydurilic acid, is described.

2. Dichlorohydurilic acid was caused to react with potassium amide in liquid ammonia at room temperature. Alloxan monohydrate was obtained in addition to five other products of undetermined character.

3. The reaction between hydurilic acid and sodium nitrite

was studied. The chief products are sodium violurate monohydrate and alloxan.

4. N-Tetramethyl-5,5'-dichlorohydurilic acid was treated with sodium nitrite. The products of this reaction were sodium dimethylviolurate trihydrate and dimethyl alloxan.

5. It was found that tetramethyldichlorohydurilic acid does not react with silver nitrite.

6. The reaction between tetramethyldichlorohydurilic acid and sodium amide in liquid ammonia was studied at room temperature. The reaction did not yield the desired 5,5'-diaminotetramethylhydurilic acid.

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